PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ABL-012-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/BE 03/00192	International filing date *(day/month/year)* 07.11.2003	Priority date *(day/month/year)* 08.11.2002

International Patent Classification (IPC) or both national classification and IPC
C07K16/28

Applicant
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1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.06.2004	23.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Le Flao, K Telephone No. +31 70 340-1040

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BE 03/00192

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-73 as originally filed

Claims, Numbers

1-49 as originally filed

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of: —.

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 22-24

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 22-24

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-21,25-49
	No: Claims	1
Inventive step (IS)	Yes: Claims	
	No: Claims	2-21,25-49
Industrial applicability (IA)	Yes: Claims	1-21,40-49
	No: Claims	25-39

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 22-24 relate to a product defined by reference to a desirable characteristic or property, namely "an unknown agent that modulates the binding of an anti-TNF-alpha polypeptide of any of claims 1 to 11, and 13 to 16 to Tumor Necrosis Factor-alpha" (claim 22) and "an unknown agent that modulates Tumor Necrosis Factor-alpha-mediated disorders" (claim 23). The scope of claims 22-24 is unclear and speculative within the meaning of Article 6 PCT. Said claims lack indication concerning their technical features. The available experimental data actually relate to anti-TNF-alpha single domain antibodies and their preparation, but not to an agent that modulates their binding. Consequently no search has been carried out for the claims 22-24 and opinion with regard to novelty, inventive step and industrial applicability will not be established.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

NOVELTY

Reference is made to the following documents:

D1: WO 91/02078 A (PEPTIDE TECHNOLOGY LTD) 21 February 1991 (1991-02-21)
D2: VALLE E ET AL: 'Infliximab' EXPERT OPINION ON PHARMACOTHERAPY, vol. 2, June 2001, pages 1015-1025, XP002965315 ISSN: 1465-6566
D3: WO 02/057445 A (MURUGANANDAM ARUMUGAM ;STANIMIROVIC DANICA (CA); NARANG SARAM (CA)) 25 July 2002

D1 discloses monoclonal antibodies anti-TNF-alpha. The possibility that these antibodies are single domain antibodies is mentioned (p.3, l.28 - p.4, l.24 ; p.15, l.25 - l.33). The subject-matter of claim 1 dealing with an anti-TNF-alpha polypeptide comprising at least one anti-TNF-alpha single domain antibody is therefore not novel over D1.

INVENTIVE STEP

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 2-17 and 21-49 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art to the subject-matter of claim 2, and discloses (cf the references above) monoclonal antibodies against TNF-alpha and how single domain antibodies can be obtained from these antibodies. The subject-matter of claim 2 relates to a single domain antibody having a specific sequence represented by any of SEQ ID NOs: 1 to 16 and 79 to 84. It differs from D1 by the specific structures given by the sequences. These structures are associated with various effects (see the description, p.51, l.4 to p.52, l.18) among them different solubility (VHH 3E, 3G and 7B having advantageous characteristics), and different antagonistic effect (3E and 3G being more potent antagonists then 1A (moderate antagonistic effect) or then 7B (no antagonistic effect)). Some of these effects are summarised on figure 2.

The problem to be solved by the present invention may therefore be regarded as the provision of alternative anti-TNF-alpha single domain antibodies. The solution proposed in claim 2 appears to solve the problem posed. However since only six clones, VHH 1A, 2B, 3E, 3G, 7B and 12B (ie those corresponding to the sequences SEQ ID NOs: 1-5 and 14) were characterized, no effect was shown to be associated with the 16 clones that were not characterized. As there is no demonstrated technical effect linked to the 16 not characterized clones, these 16 clones cannot be considered to solve the problem posed, then leading to the conclusion that the subject-matter of claim 2 cannot be considered to be inventive.

While considering the part of claim 2 that is considered to solve the problem posed, ie the part dealing with the six characterized clones VHH 1A, 2B, 3E, 3G, 7B and 12B, it is considered that it does not involve an inventive step for the following reasons. Preparing single domain antibodies in llamas or camels is a known alternative to other forms of single domain antibodies that provides different advantages as disclosed in document D2 (see the abstract : soluble and functional bispecific and bivalent antibodies with the expression levels, ease of purification, the solubility and the binding capacity of the recombinant proteins being comparable with those of the constituent monomers). Therefore it is considered that a skilled person, when trying to solve the problem posed, would have used the technique of generating camelidae single domain antibodies which would have resulted in the antibodies as claimed without using inventive skills. Characterising the single domain antibodies with the sequences render the single domain antibodies novel but not inventive over the prior art. The solubility and the antagonising properties are not unexpected effects

which could warrant recognition of an inventive step.

The dependent claims 3-11 and claims 12-21 and 25-49, referring to any of claims 1 to 11 do not appear to contain any additional features which, in combination with the features of claim 1, involve an inventive step as the relevant subject matter is either disclosed in the cited prior art of falls within the knowledge and ability of the skilled person. Document D3 discloses the therapeutical use of an anti-TNF-alpha antibody for treating rheumatoid arthtis and Crohn's disease, which anticipates the subject-matter of claims 25-39 and 49.

INDUSTRIAL APPLICABILITY

For the assessment of the present claims 25-39 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLARITY

Claims 18-20 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claims 18-20 attempt to define the subject-matter ("a method for identifying an agent") in terms of result to be achieved ("under conditions permitting binding between said polypeptide and target") without indicating what are the technical features of the method.